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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07K 5/023, C07C 237/04, C07D 215/4, A61K 38/55 — A2

(11) International Publication Number: WO 96/16079

(43) International Publication Date: 30 May 1996 (30.05.96)

(21) International Application Number: PCT/JP95/02389

(22) International Filing Date: 24 November 1995 (24.11.95)

(30) Priority Data:
6/290132 24 November 1994 (24.11.94) JP

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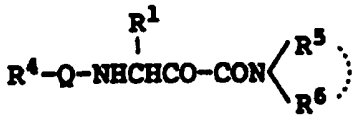
(81) Designated States: AL, AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, LS, MW, SD, SZ, UG).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: ALPHA-KETOAMIDE DERIVATIVES AS CATHEPSIN L INHIBITOR



(Ia)

(57) Abstract

The present invention relates to a cathepsin L inhibitor comprising a compound of general formula (Ia), wherein Q represents a direct bond or 1 or 2 amino acid residues that may be substituted; R^1 represents a hydrogen atom or a hydrocarbon group or heterocyclic group that may be substituted; R^4 represents an acyl group or a carboxyl group that may be esterified and R^5 and R^6 independently represent a hydrogen atom or a hydrocarbon group or heterocyclic group that may be substituted or R^5 and R^6 may bind together to form a ring; or a salt thereof, which has strong bone resorption-suppressing action and is useful for preventing or treating osteoporosis.

DESCRIPTION

ALPHA-KETOAMIDE DERIVATIVES AS CATHEPSIN L INHIBITOR

Technical Field

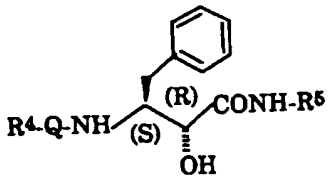
This invention relates to a cathepsin L inhibitor comprising an α-ketoamide derivative or a salt thereof as an active ingredient, and use thereof.

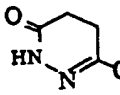
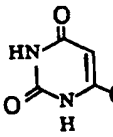
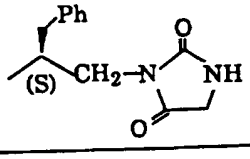
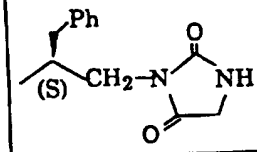
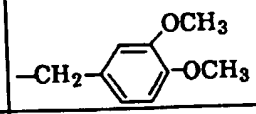
Background Art

Osteoporosis is a pathologic state or disease involving some symptom or risk due to quantitative bone reduction exceeding a certain degree. Major symptoms are spinal kyphosis, fractures of dorsolumbar bones, vertebral centra, femoral necks, lower end of radius, ribs, upper end of humerus, and others. In normal bone tissue, bone destruction occurs continuously, but there is good balance between bone formation and resorption; osteoblasts and osteoclasts play key roles in bone formation and bone resorption, respectively. Upon deterioration of this balance, bone resorption surpasses bone formation, resulting in quantitative bone reduction. Drugs suppressing bone resorption are therefore expected to serve well in preventing and treating osteoporosis. Traditionally, bone resorption-suppressing agents, such as estrogens and calcitonin have been used to treat osteoporosis. However, these therapeutic agents fail to achieve satisfactory effect in some cases, due to subject limitations or uncertain efficacy. There is therefore need of a new prophylactic/therapeutic method for accentuated bone resorption.

It has recently been shown that cathepsin L, a protease secreted by osteoclasts in the process of bone resorption, is integrally involved in the decomposition of collagen, a bone-supporting protein (FEBS Lett., Vol. 321, p. 247, 1993). Presumably therefore, bone collagen decomposition due to bone resorption can be prevented by

Table 4



No. of R. Ex.	R4-Q-	R5	m.p. (°C)	Optical Rotation $[\alpha]_D$
23	$(C_3H_7)_2CH$-L-Val-	$-CH_2Ph$	203-204[1)]	-30.3°(c=0.81,DMSO)
24	 CO-L-Leu-	$-CH_2Ph$	198-199	-27.1°(c=0.69,DMSO)
25	 CO-L-Leu-	$-CH_2Ph$	178-179[2)]	-13.1°(c=0.78,DMSO)
26	Cbz-L-Leu-		228-230[1)]	-32.5°(c=0.57,DMSO)
27	2-Qnl-L-Leu-		164-165[1)]	+3.1°(c=0.78,DMSO)
28	 CO-L-Leu-		206-207[1)]	-51.9°(c=0.51,CH_3OH)
29	Cbz-L-Leu-L-Leu-	$-CH_2Ph$	215-217[2)]	-32.2°(c=0.83,DMSO)
30	2-Qnl-L-Leu-L-Leu-	$-CH_2Ph$	127-128	+14.8°(c=0.58,CH_3OH)
31	 CO-L-Ile-	$-CH_2Ph$	209-210	-15.2°(c=0.45,DMSO)

1) 1/2hydrate, 2) 1/4hydrate
Val=valine, Leu=leucine, Ile=isoleucine,
DMSO=dimethylsulfoxide, Ph=phenyl, Cbz=benzyloxycarbonyl,
2-Qnl=quinoline-2-carbonyl

Reference Example 32

To a solution of (3S,2R)-3-amino-2-hydroxy-4-phenylbutyric acid methyl ester (3.3 g) and N-benzyloxycarbonyl-L-valine (4.2 g) in N,N-dimethylformamide (DMF) (40 ml), 1-hydroxybenzotriazole (HOBt) (2.7 g) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSCD·HCl) (3.4 g) were added under ice cooling conditions. After stirring at room temperature for 18 hours, the reaction mixture was poured over ice-water and extracted with ethyl acetate. The ethyl acetate layer was washed by sequential additions of water, an aqueous citric acid solution, water, an aqueous $NaHCO_3$ solution and saline and dried ($MgSO_4$). After the solvent was distilled off under reduced pressure, the resulting solid was filtered and washed with ethyl acetate-hexane to yield (2R,3S)-3-[N-[N-benzyloxycarbonyl-L-valyl]amino]-2-hydroxy-4-phenylbutyric acid methyl ester.

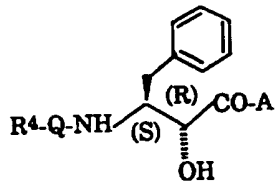
Melting point: 131-132°C

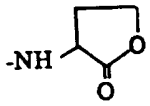
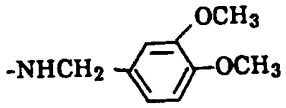
$[\alpha]_D$ = -98.3° (c=0.33, CH_3OH).

Reference Examples 33-37

By substantially the same procedure as in Reference Example 32, compounds shown in Table 5 were produced.

Table 5



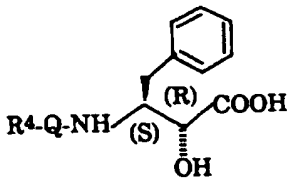
No. of R. Ex.	R4-Q-	A	m.p. (°c)	Optical Rotation $[\alpha]_D$
33	Cbz-L-Val-	$-NHCH_2Ph$	171 - 172	-21.0°(c= 0.87,CH_3OH)
34	Cbz-L-Leu-	$-OCH_3$	107 - 108	-101.5°(c= 0.94,CH_3OH)
35	Cbz-L-Leu-		201 - 202	-52.8°(c= 0.77,DMSO)
36	Cbz-L-Leu-	$-NHCH_2Ph$	173 - 174	-27.7°(c= 0.78,DMSO)
37	Cbz-L-Leu-		142 - 143	-27.1°(c= 0.80,CH_3OH)

Val=valine, Leu=leucine, Ph=phenyl, Cbz=benzyloxycarbonyl, DMSO=dimethyl sulfoxide

Reference Examples 38 and 39

By substantially the same procedure as in Reference Example 9, compounds shown in Table 6 were produced.

Table 6



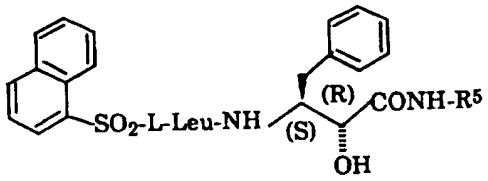
No. of R. Ex.	R4-Q-	m.p. (°C)	Optical Rotation $[\alpha]_D$
38	Cbz-L-Val-	188-189	-63.7°(c=0.87,CH_3OH)
39	Cbz-L-Leu-	141-142	-89.6°(c=0.85,CH_3OH)

Val=valine, Leu=leucine, Cbz=benzyloxycarbonyl, DMSO=dimethyl sulfoxide

Reference Examples 40 and 41

By substantially the same procedure as in Reference Example 1, compounds shown in Table 7 were produced.

Table 7



No. of R. Ex.	R5	m.p. (°C)	Optical Rotation $[\alpha]_D$
40	benzyl	181-182	-49.0°(c=0.74, dimethyl sulfoxide)
41	3,4-dimethoxybenzyl	102-103[1)]	-135.1°(c=0.62,methanol)

1) 1/2hydrate

Reference Example 42

To a solution of N-benzyloxycarbonyl-L-phenylalaninol (2.0 g), triphenylphosphine (Ph_3P) (1.9 g), hydantoin (0.71 g) and tetrahydrofuran (THF) (50 ml), diethyl azodicarboxylate (DEAD) (1.24 g) was added dropwise under

ice cooling conditions. After stirring at room temperature for 16 hours, the reaction mixture was poured over ethyl acetate and washed by sequential additions of water, an aqueous $NaHCO_3$ solution and brine, and dried ($MgSO_4$). After the solvent was distilled off under reduced pressure, the resulting residue was subjected to silica gel column chromatography and eluted with ethyl acetate-hexane (3:1, v/v) to yield 1-[(2S)-2-(N-benzyloxycarbonylamino)-3-phenylpropyl]hydantoin (1.15 g, 44%).

Melting point: 159-160°C

$[\alpha]_D$ = +15° (c=0.79, CH_3OH).

Preparation Examples

A cathepsin L inhibitor comprising inventive compound (I) or (Ia) or a salt thereof as an active ingredient can, for example, be produced with the following formulations:

1. Capsules

(1) N-(p-diethylphosphonomethylcinnamoyl)-L-isoleucyl-(3S)-3-amino-2-oxo-4-phenylbutyric acid benzylamide	10 mg
(2) Lactose	90 mg
(3) Microcrystalline cellulose	70 mg
(4) Magnesium stearate	10 mg
Total	180 mg per capsule

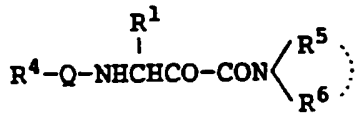
Components (1), (2) and (3) and a half portion of component (4) are mixed and granulated. To these granules, the remaining portion of component (4) is added, and the whole mixture is packed in a gelatin capsule.

2. Tablets

(1) N-benzyloxycarbonyl-L-isoleucyl-(3S)-3-amino-2-oxo-4-phenylbutyric acid benzylamide	10 mg
(2) Lactose	35 mg
(3) Corn starch	150 mg
(4) Microcrystalline cellulose	30 mg
(5) Magnesium stearate	5 mg

CLAIMS

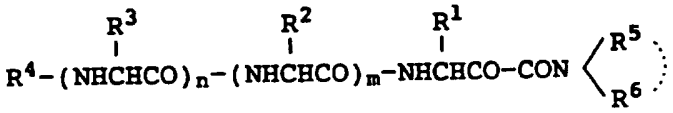
1. A cathepsin L inhibitor comprising a compound of the formula (Ia):



(Ia)

wherein Q represents a direct bond or 1 or 2 amino acid residues that may be substituted; R^1 represents a hydrogen atom or a hydrocarbon or heterocyclic group that may be substituted; R^4 represents an acyl group or a carboxyl group that may be esterified and R^5 and R^6 independently represent a hydrogen atom or a hydrocarbon or heterocyclic group that may be substituted or R^5 and R^6 may bind together to form a ring; or a salt thereof.

2. A cathepsin L inhibitor of claim 1, wherein the compound is one of the formula (I):



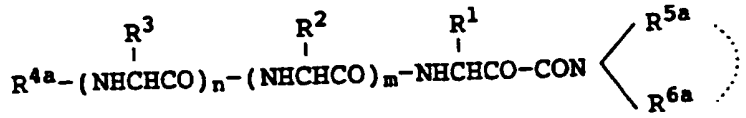
(I)

wherein R^1, R^2 and R^3 independently represent a hydrogen atom or a hydrocarbon or heterocyclic group that may be substituted; R^4 represents an acyl group or a carboxyl group that may be esterified and R^5 and R^6 independently represent a hydrogen atom or a hydrocarbon or heterocyclic group that may be substituted or R^5 and R^6 may bind together to form a ring; m and n independently represent 0 or 1; or a salt thereof.

3. A method for inhibiting a cathepsin L activity of a mammal which comprises administering to said mammal a pharmaceutically effective amount of a compound of the formula (Ia) in claim 1.

4. Use of a compound of the formula (Ia) in claim 1 for the manufacture of a medicament to be used as a cathepsin L inhibitor.

5. A compound of the formula (I')



(I')

wherein R^1, R^2 and R^3 independently represent a hydrogen atom or a hydrocarbon or heterocyclic group that may be substituted; R^{4a} is a group represented by the formula -COR^a or -SO_2R^b wherein R^a and R^b are independently an optionally substituted aryl or aromatic heterocyclic group; R^{5a} and R^{6a} independently represent a straight-chain or branched C_{1-6} alkyl group which may be substituted with an optionally substituted aryl or aromatic heterocyclic group or an optionally esterified carboxyl group and m and n independently represent 0 or 1; provided that where R^a is an optionally substituted aromatic heterocyclic group, R^{5a} and R^{6a} independently represent a straight-chain or branched C_{1-6} alkyl group which is substituted with an optionally substituted aryl or aromatic heterocyclic group or an optionally esterified carboxyl group; or a salt thereof.

6. A compound of claim 5, wherein R^1, R^2 and R^3 independently represent a hydrogen atom or (A) a hydrocarbon group selected from the group consisting of C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkinyl, C_{3-12} cycloalkyl, C_{5-12} cycloalkenyl, C_{5-12} cycloalkadienyl, C_{3-7} cycloalkyl-C_{1-8} alkyl, C_{5-7} cycloalkenyl-C_{1-8} alkyl and C_{6-14} aryl or (B) a heterocyclic group selected from the group consisting of a 5- to 7-membered aromatic heterocyclic group containing 1 atom of sulfur, nitrogen and oxgen, 5- or 6-membered aromatic heterocyclic group containing 2 to 4 atoms of nitrogen or 5- or 6-membered aromatic heterocyclic group

containing 1 or 2 atoms of nitrogen and 1 atom of sulfur and oxgen which may be condensed with a 6-membered ring containing 2 or fewer atoms of nitrogen, a benzene ring or a 5-memebred ring containing 1 atom of sulfur and a 5- to 7-membered non-aromatic heterocyclic group containing 1 atom of sulfur, nitrogen and oxgen or 4- to 7-membered non-aromatic heterocyclic group containing 1 atom of nitrogen and 3 or fewer atoms selected from nitrogen, oxgen and sulfur which may be condensed with a benzene ring, a 6-membered ring containing 2 or fewer atoms of nitrogen, or a 5-membered ring containing 1 atom of sulfur which hydrocarbon or heterocyclic group may have 1 to 3 substituents selected from the group consisting of (i) a C_{6-14} aryl group which may be substituted with hydroxy, C_{1-3} alkoxy, halogen or C_{1-3} alkyl, (ii) a C_{3-7} cycloalkyl or C_{3-6} cycloalkenyl group which may be substituted with hydroxy, C_{1-3} alkoxy, halogen or C_{1-3} alkyl, (ii) a C_{3-7} cycloalkyl or C_{3-6} cycloalkenyl group which may be substituted with hydroxy, C_{1-3} alkoxy, halogen or C_{1-3} alkyl, (iii) a heterocyclic group selected from the group consisting of a 5- to 7-membered aromatic heterocyclic group containing 1 atom of sulfur, nitrogen or oxgen, 5- or 6-membered aromatic heterocyclic group containing 2 to 4 atoms of nitrogen or 5- or 6-membered aromatic heterocyclic group containing 1 or 2 atoms of nitrogen and 1 atom of sulfur or oxgen which may condense with a 6-membered ring containing 2 or fewer atoms of nitrogen, a benzene ring or a 5-memebred ring containing 1 atom of sulfur and a 5- to 7-membered non-aromatic heterocyclic group containing 1 atom of sulfur, nitrogen or oxgen or 4- to 7-membered non-aromatic heterocyclic group containing 1 atom of nitrogen and 3 or fewer atoms selected from nitrogen, oxgen and sulfur which may condense with a benzene ring, a 6-membered ring containing 2 or fewer atoms of nitrogen, or a 5-membered ring containing 1 atom of sulfur which heterocyclic group may be substituted with C_{1-3} alkyl, (iv)

carboxyl, (C_{1-6} alkoxy) carbonyl, (C_{6-10} aryloxy)carbonyl or (C_{7-13} ararkyloxy)carbonyl, (v) a carbamoyl group which may be substituted with C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{6-10} aryl or C_{7-13} ararkyl, (vi) an amino group which may be substituted with C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{6-10} aryl or C_{7-13} ararkyl, (vii) a hydroxyl gorup which may be substituted with C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{6-10} aryl or C_{7-13} ararkyl, (viii) a thiol group which may be substituted with C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{6-10} aryl or C_{7-13} ararkyl, (ix) halogen and (x) a phosphono group which may be substituted with C_{1-6} alkyl or C_{1-6} alkoxy;
R^a and R^b are independently (A) a C_{6-10} aryl group or (B) a 5- to 7-membered aromatic heterocyclic group containing 1 atom of sulfur, nitrogen or oxgen, 5- or 6-membered aromatic heterocyclic group containing 2 to 4 atoms of nitrogen or 5- or 6-membered aromatic heterocyclic group containing 1 or 2 atoms of nitrogen and 1 atom of sulfur or oxgen which may be condensed with a 6-membered ring containing 2 or fewer atoms of nitrogen, a benzene ring or a 5-memebred ring containing 1 atom of sulfur in which the aryl or heterocyclic group may be substituted with C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy or halogen;
R^{5a} and R^{6a} independently represent a straight-chain or branched C_{1-6} alkyl group which may be substituted with (A) a C_{6-10} aryl group, (B) a 5- to 7-membered aromatic heterocyclic group containing 1 atom of sulfur, nitrogen or oxgen, 5- or 6-membered aromatic heterocyclic group containing 2 to 4 atoms of nitrogen or 5- or 6-membered aromatic heterocyclic group containing 1 or 2 atoms of nitrogen and 1 atom of sulfur or oxgen which may be condensed with a 6-membered ring containing 2 or fewer atoms of nitrogen, a benzene ring or a 5-memebred ring containing 1 atom of sulfur in which the aryl or heterocyclic group may be substituted with C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy or halogen, or (C) carboxy, (C_{1-6}

alkoxy)carbonyl, (C_{6-10} aryloxy)carbonyl or (C_{7-13} ararkyloxy)carbonyl.

7. A compound of claim 5, wherein the aryl group for R^a and R^b is naphthyl.

8. A compound of claim 5, wherein the aromatic heterocyclic group for R^a and R^b is quinolyl.

9. A compound of claim 5, wherein one of R^{5a} and R^{6a} is a hydrogen atom and the other is benzyl.

10. A compound of claim 5, wherein R' is a straight-chain or branched C_{1-6} alkyl group which is substituted with a phenyl gorup.

11. A compound of claim 5, wherein R^2 and R^3 are independently a straight-chain or branched C_{1-6} alkyl gorup.

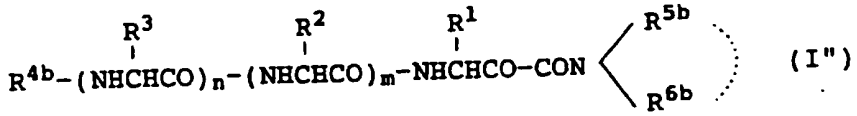
12. A compound of N-(quinoline-2-carbonyl)-L-isoleucyl-(3S)-3-amino-2-oxo-4-phenylbutanoic benzylamide, or a salt thereof.

13. A compound of N-[N-(6-oxo-1,4,5,6-tetrahydropyridazine-3-carbonyl)-L-leucyl]-(3S)-3-amino-2-oxo-4-phenylbutyric acid benzylamide, or a salt thereof.

14. A compound of N-benzyloxycarbonyl-L-leucyl-L-leucyl-(3S)-3-amino-2-oxo-4-phenylbutyric acid benzylamide, or a salt thereof.

15. A compound of N-(quinoline-2-carbonyl)-L-leucyl-L-leucyl-(3S)-3-amino-2-oxo-4-phenylbutyric acid benzylamide, or a salt thereof.

16. A compound of the formula (I")

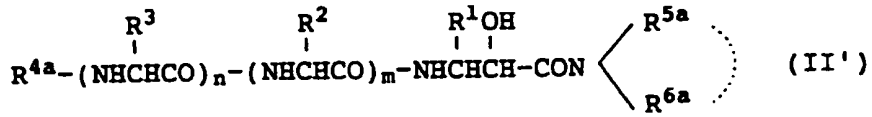


(I")

wherein R^1, R^2 and R^3, whether identical or not, independently represent a hydrogen atom or a hydrocarbon group or heterocyclic group that may be substituted; R^{4b} is represented by the formula $-COR^c$ wherein R^c is a straight-

chain or branched C_{1-6} alkyl group which is substituted with an optionally substituted aryl or aromatic heterocyclic group; R^{5b} and R^{6b} independently represent a straight-chain or branched C_{1-6} alkyl group which is substituted with an optionally substituted aryl group or an esterified carboxyl group; and m and n independently represent 0 or 1; or a salt thereof.

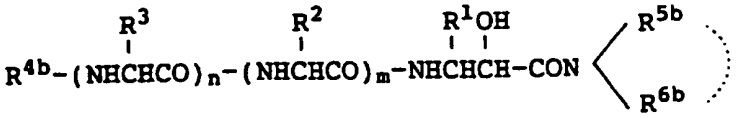
17. A method of producing a compound of claim 5 which comprises subjecting a compound of the formula (II')



(II')

wherein R^1, R^2 and R^3 independently represent a hydrogen atom or a hydrocarbon group or heterocyclic group that may be substituted; R^{4a} is a group represented by the formula $-COR^a$ or $-SO_2R^b$ wherein R^a and R^b are independently an optionally substituted aryl or aromatic heterocyclic group and R^{5a} and R^{6a} independently represent a straight-chain or branched C_{1-6} alkyl group which may be substituted with an optionally substituted aryl or aromatic heterocyclic group or an optionally esterified carboxyl group; provided that where R^a is an optionally substituted aromatic heterocyclic group and R^{5a} and R^{6a} independently represent a straight-chain or branched C_{1-6} alkyl group which is substituted with an optionally substituted aryl or aromatic heterocyclic group or an optionally esterified carboxyl group; or a salt thereof, to an oxidation reaction.

18. A method of producing a compound of claim 16 which comprises subjecting a compound of the formula (II")



(II'')

wherein R^1, R^2 and R^3 independently represent a hydrogen atom or a hydrocarbon group or heterocyclic group that may be substituted; R^{4b} is a group represented by the formula -COR^c wherein R^c is a straight-chain or branched C_{1-6} alkyl group which is substituted with an optionally substituted aryl or aromatic heterocyclic group and R^{5b} and R^{6b} independently represent a straight-chain or branched C_{1-6} alkyl group which is substituted with an optionally substituted aryl group or an esterified carboxyl group; or a salt thereof, to an oxidation reaction.

19. A composition which comprises a compound of claim 5.

20. A composition which comprises a compound of claim 16.